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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,736	01/06/2004	Robert Vincent Martinez	WYE-031	2977

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EXAMINER	
YAO, LEI	
ART UNIT	**PAPER NUMBER**
1642	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/751,736	MARTINEZ ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/24/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Arguments

The Amendment filed on 6/11/2007in response to the previous Non-Final Office Action (3/9/2007) is acknowledged and has been entered.

Claims 3, 4, and 8-20 have been cancelled previously. Claims 1, 2, and 5-7 are pending and are under consideration. It is noted that in the response filed 6/11/2007, applicant argues (On page 4 of the remarks):

> "claim 7 has never been limited to the use of GPR49 polypeptides; rather, the method of claim 7 uses the detection of an expression profile of one or more colon cancer genes, wherein one of said one or more colon cancer genes is GPR49. Although one could detect a GPR49 polypeptide when detecting an expression profile of a GPR49 gene, one could also detect a GPR49 nucleic acid. Applicants submit that the application provides direct evidence that the invention of claim 7 works as described".

The argument has been carefully considered but is deemed not to be persuasive. Although claim 7 is a broad claim comprising the method step of detecting a gene expression profile of GPR49, such as RNA expression, the Office action on bridging page 7-8 has clearly and here again states that applicant originally elected invention of a method for detecting the levels of the polypeptide encoded by a colon cancer gene, GPR49 (SEQ ID NO: 84) for examination. Thus, in current application, together with claims 1, 2, 5, and 6, the method of claim 7 is examined only for detecting the level of GPR49 polypeptides, not the levels of GPR49 mRNA, in colon samples. Applicant is suggested to file a divisional application in order to continue to examine the mRNA expression of such gene if applicant considers that it is necessary. Because detecting mRNA expression of GPR49 in colon cancer sample is not original presentation the Office could not switch the examination or expand the examination to the invention, which is not originally presented during the middle of prosecution. Thus, claim 7 remain rejected under 35 U.S.C. 101/112 1st paragraph and 112 2nd paragraph for the reasons previously set forth in the action mailed 3/9/2007 pages 2-8. Applicant is reminded that claim 7 is and will be examined only as it is drawn to the elected invention in this and future prosecution of application.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 5/24/2007 are/is considered by the examiner and initialed copies/copy of the PTO-1449 are/is enclosed.

Response to Applicant's Arguments

Rejection under 35 USC § 101/112 1st paragraph

Claims 1, 2, and 5-7 remain rejected under 35 U.S.C. 101 for the reasons previously set forth in the action mailed 3/09/2007, pages 2-6, because the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility and rejected under 35 U.S.C 112, 1st paragraph as failing to comply with the enablement requirement for claimed invention and stated again below.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, and 5-7 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility.

Claims are drawn to a method of diagnosing or monitoring colon cancer in a subject comprising the steps of detecting and comparing over expressed level of a GPR49 polypeptide or expression profile comprising CPR49 polypeptide in biological samples of a subject.

The specification teaches that 495 genes were found two fold expression in cancer tissues and 63 genes are over expressed in colon cancer tissues compared to normal colon tissues determined by microarray (RNA levels, para 433). The specification, on para 374-376, contemplates a method for detecting colon cancer in a biological sample by quantifying the amount of expression or activity of colon cancer gene in a biological sample. The specification, on paragraph 118, teaches that gene GPR49 (G protein-coupled receptor 49) is an orphan-G protein coupled receptor with an unknown ligand and express in brain, skeletal muscle, placenta and spinal cord. The specification is silent on the levels of GPR49 expression in normal colon tissue. Based on the microarray data, application claims a method of diagnosing or monitoring colon cancer in a subject comprising detecting GPR49 protein in a biological sample of a subject. However, the specification neither teaches the levels of GPR49 protein in the colon cancer tissues compared to normal tissues, nor teaches a correlation between the levels of detected mRNA in microarray and levels of its coding protein in these tissues. The only statement or "evidence" showing the correlation between the levels of mRNA and protein of GPR49 colon cancer is the declaration filed on1/10/2007 by a co-inventor Dr. R. Dr. Martinez, who states that elevated levels of mRNA in colon cancer tissue compared to disease-free colon tissue would also have elevated amounts of the polypeptide encoded by that mRNA in colon cancer tissue, however, no data or other objective evidence was provided in the declaration.

The instant claims are drawn to a method of diagnosing or monitoring colon cancer in a subject comprising the step of detecting a level of a GPR49 polypeptide in a biological sample. In order to fulfill the requirements of 35 U.S.C. 101, said method must be indicative of a specific, substantial and credible utility. A substantial utility, by definition, is a utility that defines "real world" use, and a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use is not a substantial utility. In the instant case, the overexpressed mRNA expression associated colon cancer

suggests a potential for diagnosis purpose, which, at the most, is an interesting invitation for further research and confirmation as it is not a practical method for "real world" use, and it requires significant further research and experimentation in order to form a useful and practical diagnosis method, which, by no means, is a routine or conventional experimentation. These further research and experimentation, however, is part of the act of invention, and until it has been undertaken, the utility of claimed invention is not considered substantial.

In *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), the Court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. ... a patent is not a hunting license. ... [i]t is not a reward for the search, but compensation for its successful conclusion.

The art recognizes that expression of mRNA does not dictate nor predict the translation of such mRNA into a polypeptide. For examples, the abstract of Brennan et al., (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teaches that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. The abstract of Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. The abstract of Powell et al., (Pharmacogenetics, 1998, Vol. 8, pp. 411-421) teaches that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. In this event although the mRNA of DNA 59610 was demonstrated to be overexpressed in uterine endometrial adenocarcinoma samples, according the teachings in the art, said demonstration cannot be relied upon to anticipate that the protein of SEQ ID NO: 6 would be similarly overexpressed in same cancer cells.

More evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels are following: The abstract of Hell et al., (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teaches that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. The abstract of Carrere et al., (Gut, 1999, vol. 44, pp. 545-551) teaches an absence of correlation between protein and mRNA levels for the Reg protein. The abstract of Guo et al., (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teaches that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both transcriptional and post-translational level. These references serve to demonstrate that levels polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Further, the abstract of Jang et al., (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483) teaches that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation.

Since there is not evidence showing the expression of protein or polypeptide GPR49 in colon or normal tissues, since the specification has not correlated the levels of GPR49 protein or polypeptide with the expression of mRNA, instant methods reciting diagnosing or monitoring colon cancer in a subject comprising the steps of detecting and comparing over expressed level of a GPR49 polypeptide and expression profile comprising GPR49 in biological samples do not meet the requirement of 35 U.S.C. 101.

If a molecule is to be used as a surrogate for a disease state some specific disease state must be identified in some way with the polynucleotide or polypeptide encoded therefrom. There must be some expression pattern or evidence of altered form that would allow the claimed polypeptides to be used in a diagnostic manner. However, in the absence of any disclosed relationship between the expression of protein and any disease or disorder, any information obtained in an effort to establish a differential expression pattern would constitute further research on establishing a specific, substantial, and credible utility for the method reliant on the presence of the GPR49 protein in cancer and normal colon tissue. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing". Therefore, without objective evidence that indicate differential expression of GPR49 protein in colon cancer tissue compared to normal colon tissue, the instant claims lack of specific, substantial, and credible asserted utility.

Claims 1, 2, and 5-7 remain and are again rejected under 35 U.S.C. 112, first paragraph as final office action dated 7/10/06. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

It is noted that one skilled in the art have recognized at time of invention filed that GPR49 gene is up-regulated in colon cancer (Gaitanaris et al., PG Pub 20006/0134109, Nakamura et al., PG Pub 2006/0111314, also see below, prior art record in conclusion). However, none of the publication has disclosed a method of diagnosing colon cancer by detecting a level of GPR49 protein in biological samples comprising tissue of a subject. Since applicant has not provided objective evidence to enable claimed method, one skilled in the art would be forced undo experimentation before practice claimed invention.

Previous response to applicant's argument dated 1/10/2007 is also maintained for the reason of record as set forth on page 6-8 of the Office action dated 3/9/2007.

Rejection under 35 U.S.C. 101

The response filed 6/11/2007 has been carefully considered but is deemed not to be persuasive.

On page 2-4 of the remarks, Applicant states:

"Compliance with the utility requirement does not require the presence of working examples, nor the presentation of proof that an asserted utility works as indicated. If a specific, substantial utility is asserted in an application, the utility need only be credible"

"If the asserted utility is credible, there is no basis to challenge such a claim on the basis that it lacks utility under 35 U.S.C. 10. Here, similarly, the asserted utility is clear--diagnosing or monitoring colon cancer. It is also credible, as the application provides a reasonable basis for concluding that the invention will work".

"the application claims a very specific described utility based on the discovery that the GPR49 gene is overexpressed in colon cancer".

In response to this argument, specific utility requires that the invention have substantial utility. The invention does not have substantial utility because additional work must be done to determine if the invention has a real world use. As discussed in the rejection, a substantial utility, by definition, is a utility that defines "real world" use, and a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use is not a substantial utility. In this case, based on the microarray result overexpressed mRNA expression associated colon cancer merely suggests a potential for diagnosis purpose, which, at the most, is an interesting invitation for further research and confirmation as it is not a practical method for "real world" use, and it requires significant further research and experimentation in order to form a useful and practical diagnosis method, which, by no means, is a routine or conventional experimentation. These further research and experimentation, however, is part of the act of invention, and until it has been undertaken, the utility of claimed invention is not considered substantial. Therefore, claimed invention is not supported by specific utility. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained for the reason of record above. If applicant could submit objective evidence demonstrating the differential

expression/overexpression of the claimed protein compared to normal control would overcome this rejection.

Rejection under 35 U.S.C. 112, first paragraph

On page 5 of the remarks, applicant states (Claims 1-2 and 5-7):

> If the application provides a reasonable basis for expecting the invention to work, the enablement requirement has been satisfied. Some experimentation is acceptable, so long as it is not undue. Even if the GPR49 mRNA data were nothing more than an "invitation for further research and confirmation" by testing GPR49 protein levels in colon cancer to confirm that they are indeed elevated as predicted by the application, such is the nature of routine work in the art: the confirmatory assay would be focused (on GPR49 polypeptide levels in colon cancer) and could be performed using routine assays such as those referenced in the present application, assays that are therefore well within the level of skill in the art.

In response to this argument, rejection under 35 U.S.C. 112, first paragraph, is based on whether undue a quantity of experimentation is required for one skilled in the art to use or practice claimed invention. Applicant although provides teaching on the level of GPR49 mRNA is increased in colon sample based on the result of RNA microarray, for the reasons previously set forth, this information is enabling only for a method of diagnosing colon cancer by the step of detecting levels of GPR49 mRNA in the test sample. However, instant claims are drawn to a method of diagnosing colon cancer by the step of detecting levels of GPR49 polypeptide in the sample. In rejection stated above, the office provides strong evidence indicating predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Without objective evidence that indicate differential expression of GPR49 protein in colon cancer tissue compared to normal colon tissue, one skilled in the art would be forced a quantity of undue experimentation before practice claimed invention. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained for the reason of record.

Applicant is noted that submission of objective evidence demonstrating the differential expression/overexpression of GPR49 protein in colon cancer sample compared to normal control would overcome this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, and 5-7 remain rejected under 35 U.S.C. 112, second paragraph for the reasons previously set forth in the action mailed 3/09/2007, pages 8 and stated again below.

> Claims 1, 2, and 5-7 are vague and indefinite in the recitation of "GPR49" as the sole means of detecting and comparing the levels of polypeptide referred to in claim 1 and 7. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. This rejection can be obviated by amending the claims to specifically and uniquely identify GPR49, for example, by SEQ ID NO 84.

On page 6, applicant argues:

> The term "GPR49" is very widely used in the art. The undersigned attorney is not aware that the art uses the term to refer to any gene or protein other than "G protein-coupled receptor 49." The Examiner's concern that the use of the term in the claim leads to confusion therefore appears to be unfounded. Furthermore, Applicants submit that the use of the term in the claim cannot be ambiguous because, read in view of the present application, "GPR49" could not be understood to refer to anything other than "G protein-coupled receptor 49."

the argument has been considered but has not been found persuasive because contrary to applicant's argument, although the undersigned attorney is not aware of any gene or protein other than G protein-coupled receptor 49, applicant presents no evidence that the this lab named is not used for any other polypeptide. Further the claimed invention is not simply drawn to G protein-coupled receptor 49, but rather is drawn to "a" GPR49 polypeptide", inferring a multiplicity of GPR polypeptides wherein the specification clearly validates the indefinite nature of the claim language wherein the specification states that

[0225] In addition, the invention encompasses polynucleotide molecules which are structurally different from the molecules described above, but which have substantially the same properties as the molecules above. Such molecules include allelic variants.

[0226] DNA sequence polymorphisms leading to changes in the amino acid sequences of the proteins can exist within a population (e.g., a human population). These polymorphic DNA sequences can be used by the present invention. Such genetic polymorphism may exist among individuals within a population due to natural allelic variation. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist and may affect the overall expression level of that gene (e.g., by affecting regulation or degradation).

[0227] Polynucleotide molecules corresponding to natural allelic variants or homologs of CCGs can be isolated based on their homology to the CCGs using standard hybridization techniques under stringent or highly stringent hybridization conditions. Polynucleotide molecules corresponding to natural allelic variants or homologs of CCGs can further be isolated by mapping to the same chromosome or locus as the original CCG.

[0228] In another embodiment, a polynucleotide molecule used in the invention is at least 15, 20, 25, 30, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000 or more nucleotides in length and can hybridize under reduced stringent, stringent, or highly stringent conditions to a sequence encoded by a CCG. In one example, the isolated polynucleotide molecule can hybridize under reduced stringent, stringent, or highly stringent conditions to a sequence selected from SEQ ID NOS:1-63.

[0230] Accordingly, another aspect of the invention pertains to CCPP variants that contain changes in amino acid residues that are not essential for activity. Such variants differ in amino acid sequence from the original CCPP, yet retain biological activity of the corresponding CCPP. In one embodiment, a variant comprises an amino acid sequence with at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more sequence identity or similarity to a CCPP.

all of which appear to encompass variants of the claims GPR49 peptides and the metes and bounds of the patent protection claimed cannot be determined. Applicant's argument has not been found persuasive, and the rejection is maintained for the reason of record above. Applicant is again strongly suggested to amend claims by specifically and uniquely identify GPR49, for example, by SEQ ID NO 84.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY

SUSAN UNGAR, PH.D
PRIMARY EXAMINER